

IT IS CLAIMED:

1. A method for screening a peptoid for effectiveness in transfecting a cell with an oligonucleotide, the method comprising:

- 5 providing a plurality of different-sequence peptoids in separated compartments;
forming a peptoid-oligonucleotide mixture in at least one of said compartments;
contacting said mixture with a cell; and
determining the degree of transfection of said cell by said oligonucleotide.

- 10 2. The method of claim 1, further comprising identifying a transfecting peptoid contacted with a transfected cell.

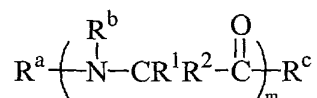
3. The method of claim 1, wherein said peptoids are supported on solid particles.

- 15 4. The method of claim 3, wherein each of said compartments contains a single particle, and each such particle has bound thereto same-sequence peptoids.

5. The method of claim 4, further comprising the step of releasing the peptoids from the particle in said at least one compartment, prior to forming said peptoid-
20 oligonucleotide mixture.

6. The method of claim 1, wherein said oligonucleotide is an antisense oligonucleotide directed against a gene product in said cell, and said determining comprises detecting an alteration in the level of expression of said gene.

- 25 7. The method of claim 1, wherein said different-sequence peptoids have the general formula I:



I

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where

R^a is selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted with one or more groups X; hydrogen, -OH, -SH, -COOH, sulfonyl, and a lipid moiety, wherein said lipid moiety may be conjugated to a linker moiety,

- 5 each R^b is independently selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted with one or more groups X; and hydrogen,

wherein at least one group R^b is not hydrogen;

- R^c is selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and
10 aralkynyl, any of which may be substituted one or more groups X; hydrogen, -OH, -SH, -NH₂, -NHR, -NH(C=O)R, where R is lower alkyl; sulfonyl, hydrazine, and a lipid moiety, wherein said lipid moiety may be conjugated to a linker moiety;

- X is selected from hydroxy, alkoxy, amino, guanidino, amidino, alkylamino, alkylthio, halogen, nitro, cyano, keto, aldehyde, carboxylic acid, carboxylic ester,
15 carboxylic amide, sulfonic acid and sulfonic ester;

R^1 and R^2 are independently selected from hydrogen, lower alkyl, and lower alkoxy; and

m is an integer selected from 2 to about 50.

- 20 8. The method of claim 7, wherein in formula I, R^a comprises a lipid moiety, and R^c is selected from -NH₂, -NHR, and -NH(C=O)R, where R is lower alkyl.

9. The method of claim 8, wherein said lipid moiety is a sterol.

- 25 10. The method of claim 7, wherein in formula I, each of R^1 and R^2 is hydrogen.

11. The method of claim 7, wherein in formula I, at least one R^b includes a group which is cationic at physiologically relevant pH, and at least one R^b is uncharged at physiologically relevant pH.

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12. The method of claim 11, wherein said cationic group is selected from aminoalkyl, ammonium, guanidino, amidino, imidazolium, pyridinium, and cationic

sidechains found on naturally occurring amino acids.

13. A method of screening a library of different-sequence peptoids for effectiveness in transfecting a cell with an oligonucleotide, the method comprising:

- 5 (i) contacting each member of the library with an oligonucleotide, to form a plurality of peptoid-oligonucleotide mixtures,
(ii) contacting each said mixture with a cell;
(iii) screening each cell for transfection of the oligonucleotide; and
(iv) identifying transfecting peptoids in mixtures contacted with transfected cells.

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14. The method of claim 13, wherein said library of peptoids is provided in an array of physically separated compartments.

15. The method of claim 13, wherein said peptoids are supported on solid
15 particles.

16. The method of claim 15, further comprising the step of releasing the peptoids from the particles in said compartments, prior to said contacting step (i).

20 17. The method of claim 15, wherein each compartment contains a single particle, and each particle contains a single peptoid.

18. The method of claim 16, wherein, prior to contacting step (i), a duplicate array of said library of peptoids is created.

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19. The method of claim 18, wherein identifying step (iv) comprises identifying peptoids in said duplicate array at positions corresponding to transfecting peptoids.

20. The method of claim 19, wherein said identifying is done by tandem mass
30 spectrometry (MS-MS).

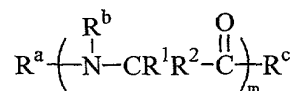
21. The method of claim 13, wherein said cells comprise distinct cell types, and said identifying is effective to identify peptoids capable of selectively delivering oligonucleotides to a selected cell type relative to a non-selected cell type.

5 22. The method of claim 21, wherein said selected cell type is a tumor cell, and said non-selected cell type is a non-tumor cell.

23. The method of claim 21, wherein said selected cell type is an endothelial cell, and said non-selected cell type is an epithelial cell.

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24. The method of claim 13, wherein said different-sequence peptoids have the general formula I:



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I

where

R^a is selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted with one or more groups X; hydrogen, -OH, -SH, -COOH, sulfonyl, and a lipid moiety, wherein said lipid moiety may be

20 conjugated to a linker moiety,

each R^b is independently selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted with one or more groups X; and hydrogen,

wherein at least one group R^b is not hydrogen;

25 R^c is selected from the group consisting of alkyl, aryl, aralkyl, aralkenyl, and aralkynyl, any of which may be substituted one or more groups X; hydrogen, -OH, -SH, -NH₂, -NHR, -NH(C=O)R, where R is lower alkyl; sulfonyl, hydrazine, and a lipid moiety, wherein said lipid moiety may be conjugated to a linker moiety;

X is selected from hydroxy, alkoxy, amino, guanidino, amidino, alkylamino, 30 alkylthio, halogen, nitro, cyano, keto, aldehyde, carboxylic acid, carboxylic ester, carboxylic amide, sulfonic acid and sulfonic ester;

R^1 and R^2 are independently selected from hydrogen, lower alkyl, and lower alkoxy; and

m is an integer selected from 2 to about 50.

5 25. The method of claim 24, wherein in formula I, R^a comprises a lipid moiety, and R^c is selected from $-NH_2$, $-NHR$, and $-NH(C=O)R$, where R is lower alkyl.

26. The method of claim 25, wherein said lipid moiety is a sterol.

10 27. The method of claim 24, wherein in formula I, each of R^1 and R^2 is hydrogen.

28. The method of claim 24, wherein in formula I, at least one R^b includes a group which is cationic at physiologically relevant pH, and at least one R^b is uncharged at physiologically relevant pH.

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29. The method of claim 28, wherein said cationic group is selected from aminoalkyl, ammonium, guanidino, amidino, imidazole, pyridinium, and cationic sidechains found on naturally occurring amino acids.

20 30. A method of determining the sequence of an analyte peptoid by tandem mass spectrometry, wherein the N-substituents on said peptoid are selected from a known population of substituents, comprising:

determining predicted molecular weights of fragments that would be produced by cleaving amide bonds in at least one theoretical peptoid, having a sequence based on

25 one combination of said known population of N-substituents;

subjecting the analyte peptoid to MS-MS fragmentation to produce a population of analyte fragment ions of various molecular weights; and

determining whether the molecular weights of said analyte fragments correspond to said predicted molecular weights.

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31. The method of claim 30, wherein predicted molecular weights of fragments are determined for a plurality of theoretical peptoids, having sequences based on different combinations of said known population of N-substituents.

- 5 32. The method of claim 31, wherein the N-substituents at one or more selected positions in the analyte peptoid are predetermined.